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Differentiation of proteins and cancer cells using metal oxide and metal nanoparticles-quantum dots sensor array

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ABSTRACT

A novel nanoparticles-quantum dots-based fluorescence sensor array has been developed for sensing proteins and cancer cells. In this study, six types of nanoparticles (NPs, including CuO, ZnO, Eu_2O_3, AuNPs, AgNPs, Au-Ag core-shell) conjugated with CdSe quantum dots (QDs) were used as sensing elements to create the multi-sensors of array. The fluorescence of quantum dots was efficiently quenched by nanoparticles. Fluorescence turn-on or further quenching could be observed due to the disruption of the nanoparticles-QDs interaction by proteins, affording distinct fluorescence response patterns. Linear discriminant analysis (LDA) was used to analyze the patterns. Moreover, protein quantification could be performed according to the fluorescence intensity on a specific or single sensing element. The linear dynamic ranges of the sensor array for proteins was in the range of 2–50 μM, and the limits of detection (LODs) was below 2 μM that varied for different proteins. Six cancer cells were also successfully differentiated by their fluorescence response patterns. This work indicates that the nanoparticles-QDs-based sensor array has a great potentials to be used in such fields as proteomics and medical diagnostics.

1. Introduction

The detection and discrimination of bioanalytes, especially proteins, are very important in clinical medicine examination and early diagnosis of diseases or even cancers. Conventional methods, such as enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) are high sensitive, however, time-consuming, high cost and impossibility of simultaneously sensing multiple bioanalytes remain problems. Over the past decades, optical chemical sensor arrays have been developed as an alternative powerful method for the detection and discrimination of bioanalytes or multiple bioanalytes [1–7]. Fluorescence-based sensor array, in particular, is extremely attractive because of its strong discriminatory power of sensing multianalytes whether in gas or liquid phase, as well as its rapid response and high sensitivity [8–10]. It has been applied in sensing a variety of bioanalytes including proteins, saccharides, nucleic acids, bacteria, and cells [11–13]. It employs a group of nonselective or semiselective fluorescent materials as sensing elements which could diversely response to analyte, generating a composite fluoresence response pattern. Some fluorescent materials can serve directly as sensing elements in an array [14], such as conjugated fluorescent polymers [15,16], functionalized porphyrins [17], fluorescent ZnL^R complexes [18], and synthetic receptors [19]. They act not only as receptors which can respond to analytes, but also as indicators which exhibit strong luminescence. When they bind to analytes, dramatic changes in the initial fluorescence intensity take place. Other fluorescent materials, such as conventional organic fluorophores, can not act directly as sensing elements. They should be modified with receptors which are diverse and have interactions with the analytes of interests. Walt DR et al. [11] have utilized beads (microspheres) stained or coated with Nile Red dyes in the distal tip of fiber optics as the sensing materials to fabricate the fibre optic microarrays for sensing vapours, nucleic acids, proteins, etc. Hamilton AD et al. have used an ensemble of fluorescent DNA G-Quadruplexes as the sensing elements for protein recognition [20]. Rotello VM et al. have used gold nanoparticles-fluorescent polymer or biopolymer complexes as sensing elements to fabricate a series of sensor arrays for sensing proteins, bacteria and cells [10,21,22]. Fan CH et al. have empolyed seven DNA strands of different sequences, structures, and lengths tagged with a fluorescent dye to develop a DNA-graphene sensor array for the identification of proteins, cells and bacteria [23]. However, most of the fluorescent materials suffer from photobleaching. And synthesizing a large number of fluorescent materials used

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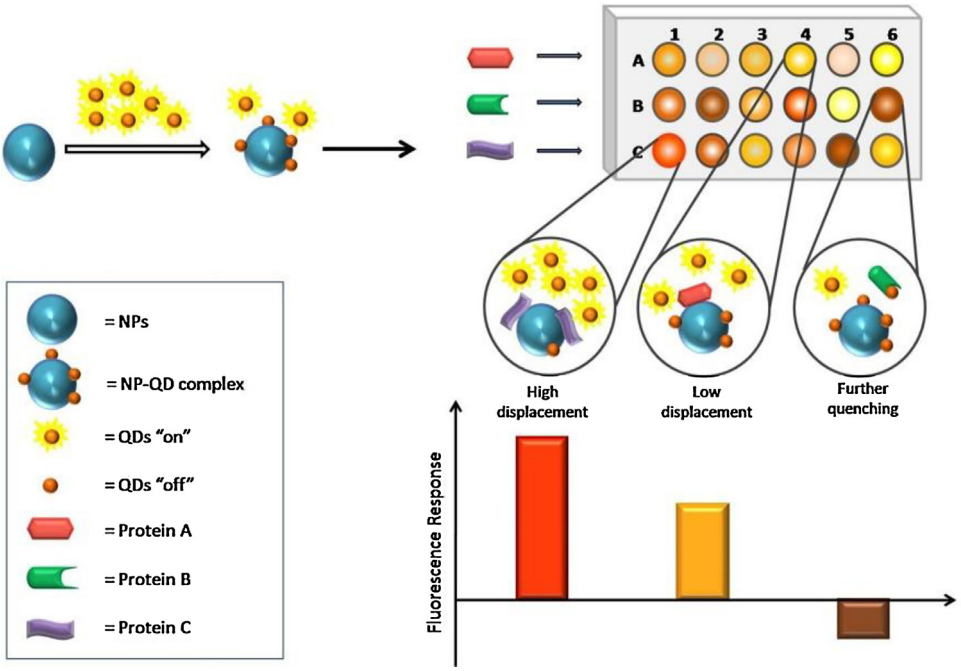

Fig. 1. Schematic diagram of the fluorescence sensor array based on six types NP-QD complexes. Nanoparticles (NPs) initially quench the fluorescence of QDs in some degree. The fluorescence of QDs is restored or further quenched due to the presence of proteins(A, B or C) disrupting the interactions between QDs and NPs.

directly as sensing elements or the search for a group of fluorescent materials modified with different receptors as sensing elements remains a challenge. Therefore, there is a need to develop a simple and efficient approach for obtaining sensing elements to fabricate a robust flourescence-based sensor array for the detection and discrimination of bioanalytes.

Quantum dots (QDs) have emerged as attractive fluorescent colloidal nanocrystals composed by semiconductor materials over the past decades. They have already been explored in chemo/biosensing due to their inherent high fluorescence quantum yields, narrow emission band, and high resistance to photobleaching, compared with conventional organic dyes or fluorescent proteins [24]. Generally, quantum dots attached with nanoparticles has been reported to show fluorescence quenching. Quite a few studies have demonstrated that nanoparticles such as noble metal nanostructures of gold nanoparticles (AuNPs) or silver nanoparticles (AgNPs), can quench the fluorescence of organic fluorescent dyes or QDs efficiently [25], forming NP-QD complex. Some have even investigated the quenching efficiency of QDs binding to AuNPs [26,27]. Interestingly, Liu JW et al. have found that some metal oxide nanoparticles (MONPs) can quench the fluorescence of a FAM (6-carboxy fluorescein) labeled DNA, when it is adsorbed on the surface of nanoparticles [28]. Based on the strategy of nanoparticles inducing fluorescence quenching, a variety of chemo/biosensors or arrays based on QDs-functionalized metal nanoparticles or organic dyes-functionalized MONPs are expected to be applied in sensing. After adding the bioanalytes such as proteins to NP-QD complex, the fluorescence of QDs could be restored because the interactions between nanoparticles and proteins which have been extensively studied [29–31], lead to the release of QDs from the NP-QD complex or further quenching of QDs due to the interaction between proteins and QDs [32]. Different metal nanoparticles or metal oxide nanoparticles have different adsorption affinities to proteins, showing the discrimination via a sensor array. Therefore, we had a strong motivation to develop a simple fluorescence sensor array using different combinations of various nanoparticles and a single fluorescent material (QDs) for bioanalytes sensing. With the advancement of nanotechnology, more and more metal nanoparticles or metal oxide nanoparticles with diverse functions will be synthesized to greatly enrich library of sensing elements to construct sensor arrays. As far as we know, the discrimination ability of an array depends on the number of sensing elements, just like the mammalian olfactory system. For example, the smell-detection capability of the canine nose is one million times more sensitive than human's, because canine has around 2 billion odorant receptors (same as the sensing elements of array), while human has only 4000.

In this study, it was found that the fluorescence of CdSe quantum dots could be quenched by nanoparticles, including three metal oxide NPs of CuO, ZnO, Eu_2O_3, and three metal NPs of AuNPs, AgNPs, Au-Ag core-shell, forming six NP-QD complexes (conjugates). After the addition of bioanalytes, the fluorescence of QDs was restored because the interactions between nanoparticles and bioanalytes make QDs release from NP-QD complex. Meanwhile, further fluorescence quenching could also be observed due to the interactions between proteins and QDs. Therefore, a simple fluorescence sensor array was designed based on different combinations of six nanoparticles and QDs as sensing elements which were CuO-QD complex, ZnO-QD complex, Eu_2O_3-QD complex, AuNP-QD complex, AgNP-QD complex, and Au-Ag-QD complex, as illustrated in Fig. 1. Linear discriminant analysis (LDA) was performed to differentiate proteins with a high degree of accuracy based on the fluorescence response patterns. The proposed sensor array was also applied in cancer cells sensing.

2. Experimental

2.1. Chemicals and materials

Chloroauric acid was purchased from Shanghai Fine Chemical Research Institute (Shanghai, China). Silver nitrate was from Shanghai Chemical Reagent Co. LTD (Shanghai, China). Sodium citrate and other chemicals were obtained from Tianjin First Chemical Reagent Factory (Tianjin, China). The analyte proteins including casein (Cas), bovin serum albumin (BSA), myoglobin (Mb), trypsin (Try), pepsin(Pep), papain (Pap), hemoglobin (Hb) and lipase (Lip)